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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/630,319	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/20/2004 and 05/31/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-93,96-101,105 and 133-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-93, 96-101, 105 and 133-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/20/2004, 08/27/2004, 08/30/2004, 10/28/2004 and 05/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Art Unit Location

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1648, Examiner Emily Le.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 08/20/2004 has been entered.

Status of Claims

3. Claims 1-89, 94-95, 102-103 and 105-132 are cancelled. Claims 133-155 are added. Claims 90-93, 96-101, 105 and 133-151 are pending and under examination.

Information Disclosure Statement

4. The Information Disclosure Statements (IDS) filed 08/20/2004, 08/27/2004, 08/30/2004, 10/28/2004 and 05/31/2005 have not been fully considered for the following reasons:

37 CFR 1.56(b) states that information is material to patentability when it is **not cumulative** to information already of record or being made of record in the application, and (1) **It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim**; or (2) It **refutes, or is inconsistent with, a position the applicant takes** in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability. [Emphasis added] A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability. It is incumbent upon patent applicants, therefore, to bring "material" information to the attention of the Office.

In the instant, a review of the all of the 15 U.S. Patent and PreGrant Patent documents listed in the IDS filed 08/20/2004 and 10/28/2004, among a total of more than 400 references cited, the Office finds that the only one reference is material to patentability, U.S. PreGrant Pub. No.20040171150; whereas, all of the other 14 references are cumulative to one another, including the cited U.S. PreGrant Publication; and the information provided in the references do not compel a conclusion that a claim is unpatentable. Thus, the Information Disclosure Statements do not comply with 37 CFR 1.56. In view of the very low percentage of references material to patentability in the sampled documents reviewed, the submission is not in compliance with 37 CFR

1.56 and 1.98. Accordingly, the remaining references will not be considered. Thus, the Information Disclosure Statements filed 08/20/2004, 08/27/2004, 08/30/2004, 10/28/2004 and 05/31/2005 have not been fully considered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 90-93, 96-101, 105 and 133-151 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 104 recites, "wherein the CpG oligonucleotide is a stabilized oligonucleotide". The recitation renders the claims indefinite. It is unclear what is intended by the cited recitation. In the instant, it is unclear what Applicant regards as a stabilized oligonucleotide. Is the recitation directed at a structural, physical or biological modification of an oligonucleotide? And what is the specific modification that is encompassed by the cited recitation?

Claims 134-135 require that the CpG oligonucleotide not to have the "'$X_1X_2CGX_3X_4$" palindrome. However, it is unclear what is intended by the recitation "$X_1X_2CGX_3X_4$". A value for X_1-X_4 is absent from the claims. What is the value of X_1-X_4?

Claim 133 requires that the CpG oligonucleotide not have a GCG trinucleotide at a 5' and/or 3' terminal. In the instant, the recitation "5' and/or 3' terminal" renders the claim indefinite. As written, it is unclear if the cited recitation is directed to encompass

the 5' and/or 3' terminal of a nucleic acid or a sequence of nucleic acids. Clarification is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 133, 135, 137 and 139 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 133 is newly added claim. Claim 133 requires that a GCG trinucleotide is absent from the CpG oligonucleotide. Applicant notes that adequate written support for the limitation(s) recited in claim 133 can be found at lines 1-20 of page 16, line 24 at page 18, lines 28-29 of page 21 and lines 1-6 of page 22.

The Office has reviewed the cited passages and the entire specification. However, the Office cannot find support for the limitation(s) recited in newly added claim 133 at the passages cited or any part of the specification.

9. Claims 90-93, 96-101, 105 and 133-151 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

The broadest claim is directed to a process for treating bacterial infection in subjects with the administration of an oligonucleotide containing the CpG motif, wherein the oligonucleotide is stabilized.

Nature of the invention:

The nature of the claimed invention is directed at treating bacterial infections with the administration of an oligonucleotide that comprises the CpG motif in vertebrates diagnosed with said infection

Breadth of the claims:

The specification defines "subject" as a human or vertebrate animal including dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat and mouse. [Lines 27-28 of page 19 of the specification.] It should be noted that the specification is not limited humans, dogs, cats, horses, cows, pigs, sheeps, goats, chickens, rats and mice.

The specification also lists examples of infectious bacteria, which includes *Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps* (e.g., *M. tuberculosis, M. avium, M. Intracellulare, M. kansaii, M gordonae*), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp.,*

Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter erogenes, Klebsiella pneuomiae, Pasturella multicoda, Bacteroides sp., Fusobacterium nucleatum, Sreptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira, and *Actinomeyces israelli.* [Paragraph bridging pages 14-15 of the specification.] It should be noted that the specification is not limiting "bacteria" to only those listed at the cited passage.

Thus, in view of the disclosure, the breadth of the claims encompasses:

- **all vertebrate animals**
- **all bacterium**
- **all nucleic acid sequences that contains the CpG motif.**

Thus, the broadest breadth of the claimed invention encompasses the use of any nucleic acid sequences containing the CpG motif to treat infections caused by all bacteria in all vertebrate animals.

State of the Art:

The art acknowledges the importance of Th1 type immune response, which stimulates the production of Th1 associated cytokines, in contributing to the elimination of intracellular pathogens such as mycobacterium and virus. However, the art also teaches that:

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, **host response to exogenously administered cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state**.

- **Both Th1 and Th2 type of immune responses in necessary.** Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, **a tight control over where and when Th1 and Th2 immune responses happen is necessary.**[1]
- The **efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial.** For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection.[2]
- **Interleukin-12**, Th1 associated cytokine, induces different effector mechanisms that result in **either protection or exacerbation**.[3] Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice.

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]

- **Interleukin 18,** a Th1 associated cytokine, is **responsible for the progression** of endotoxin-induced liver injury in mice primed with interleukin 18.[4]
- **Interleukin 6 and interferon gamma**, both are Th1 associated cytokines, **augment the susceptibility** of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utlitising **HIV-1** strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1.[5]
- **Interleukin 2**, a Th1 associated cytokine, **increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies.** Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. [6]
- **Interferon gamma is ineffective against the virulent strain of Mycobacterium avium.** Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma.[7]

In all, the art amply recognizes the following **limitations**: **inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects**.

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[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]
[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]
[7] Silva et al. Evaluation of IL-12 in immunotherapy and vaccine design in experimental Mycobacterium avium infections. The Journal of Immunology, 1998, Vo. 161, 5578-5585. [Last sentence, left column of page 5583, in particular.]

The art notes that the efficacy of exogenous cytokines capable of potentiating normal host defense mechanisms may be curtailed in immunocompromised patients lacking the pertinent effector cells or containing disease-related factors preventing lymphocyte activation. The art also notes that viral, bacterial and parasite adaptations to the presence of cytokines pose new problems and approaches based on cytokine intervention will have to take these factors into account.[8]

The CpG art teaches:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[9] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice.[10] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.
- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies.[11] The art frequently notes that the **specific nucleic acids**, purines and pyrimidines, surrounding the CpG

[8] Masihi, K., paragraph bridging left and right columns of page 646, in particular.
[9] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]
[10] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]

motif, **influence both the level and type of immune stimulation**; the **spacings** between CpG motifs surrounding the CpG motif **influence both the level and type of immune stimulation;** and the **type of cytokine stimulated** by oligonucleotides containing the CpG motif **varies from one oligonucleotide to the next.**[12, 13,14] The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence.[15]

- **In vitro observations do not accurately predict what happens in vivo.**[16]
- The **immunostimulatory activity of CpG oligonucleotides is species specific**. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.[17]
- The **immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another.**[18]

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[11] Krieg et al., paragraph that bridge pages 716-717, in particular.
[12] Mutwiri et al., last sentence of paragraph bridging pages 89-90.
[13] Ibid.
[14] Ibid, third to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[15] Krieg et al., paragraph that bridge pages 712-713, in particular.
[16] Mutwiri et al., second to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[17] Ibid, section 2.1, disclosed on page 90, in particular.
[18] Ibid, Table 1 on page 92, and first sentence in first full paragraph, left column of page 94, in particular.

- **Oligonucleotides containing the CpG motif increase the susceptibility to infection by *Candida albicans*.**[19] Ito et al. notes that although oligonucleotides containing the CpG motif promote Th1 immunity, the induction of IL-12 by the oligonucleotide increases infection by *Candida albicans* in mice, rather than protecting the mice from said infection.

Presence or absence of working examples:

The specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection.

All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif. For example, the working examples note that the immunostimulatory effect and the extent of the immunostimulatory effect induced by oligonucleotides containing the CpG motif varies with the length of the oligonucleotide containing CpG motif; the number of CpG motifs present in the oligonucleotide; the nucleic acid(s) that flanks the CpG motif; the presence or absence of a modified phosphate backbone; and the presence or absence of methylated cytosine...etc.

Additionally, the working examples set forth that the immunostimulatory effect of oligonucleotides containing the CpG motif varies from one oligonucleotide to the next.

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[19] Ito et al. CpG oligonucleotides increase the susceptibility of normal mice to infection by *Candida albicans*. Infection and Immunity, September 2005, Vol. 73, No. 9, 6154-6156. [See abstract of Ito et al.]

In addition, the working examples also demonstrate that an oligonucleotide having the sequence set forth in SEQ ID NO: 10, which contains the CpG motif is capable of stimulating the production of interleukin-12 and interferon-gamma, both of which are Th-1 associated cytokines. The working examples also demonstrate that oligonucleotides having the sequence set forth in SEQ ID NOs: 115, 19, 15, 116 and 18, all of which contains the CpG motif are capable of stimulating the production of interleukin-6, a Th-1 associated cytokine in vitro; and oligonucleotides having the sequence set forth in SEQ ID NOs: 124 and 16, which also contain the CpG motif, are not capable of inducing interleukin-6 to the extent that is higher than the control, media. Additionally, the working example shows that an oligonucleotide having the sequence set forth in SEQ ID NO: 48, which also contains the CpG motif and a modified phosphate backbone are capable of inducing interleukin-6 production in vivo.

Lastly, the working examples demonstrates that oligonucleotides having the sequence set forth in SEQ ID NOs: 28-29, 101, 104-105, 7 and 3, all of which contains the CpG motif are capable of stimulating the production of interleukin-6, tumor necrosis factor-alpha, interferon-gamma, GM-CSF, and interleukin 12, Th-1 associated cytokines in human PMBC. And oligonucleotide having the sequence set forth in SEQ ID NO: 102, which contains a CpG motif, is capable of inducing just interleukin-6, tumor necrosis factor-alpha, GM-CSF, and interleukin 12. The oligonucleotide having the sequence set forth in SEQ ID NO: 102 does not induce interferon-gamma production. Furthermore, the oligonucleotide having the sequence set forth in SEQ ID NO: 103, which contains a CpG motif, is capable of inducing just interleukin-6, interferon-gamma,

tumor necrosis factor-alpha, and GM-CSF. The oligonucleotide having the sequence set forth in SEQ ID NO: 103 does not induce production of interleukin-12.

Amount of direction or guidance presented:

Beside a discussion of how various structural modification effects the immunostimulatory activity of oligonucleotides, as exemplified by the working examples, Applicant has not provided any direction or guidance directed at the use of any of the disclosed oligonucleotides containing CpG motif to treat bacterial infections in vertebrate.

All that is gathered from the specification is the contemplation of apply the generic immunostimulatory activity that is sometimes observed with oligonucleotides containing the CpG motif, to treat, prevent, or ameliorate bacterial infection. [Lines 5-15 of page 9.] It is also noted that the specification prefers nucleic acid sequences that stimulate cytokine production, particularly IL-I, IL-12, IFN-gamma, TNF-alpha, and GM-CSF. [Lines 24-30 of page 8.]

Predictability or unpredictability of the art:

As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable. The level of immune stimulation varies from one oligonucleotide to the next. The type of cytokine stimulated by oligonucleotides containing CpG motif also varies from one oligonucleotide to the next.

In addition, as demonstrated by the cytokine art, the use of cytokines in the treatment of diseases is unpredictable. The art notes that the inherent toxicity, the

unclear pharmacological behavior, and the pleiotropic effects of cytokines contribute to the spontaneity that is observed in treatment of infections with the cytokines.

Quantity of experimentation necessary:

In the instant, Applicant has not provided a nexus between the activities observed for various oligonucleotides containing the CpG motif and bacterial infections. Applicant has not provided any guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections. Applicant has provided any guidance pertaining to the type of activity that would need to be stimulated to provide effective treatment against bacterial infections. Applicant has not provided any guidance relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections. In all, Applicant has failed to provide any guidance relating the treatment of bacterial infection with oligonucleotides containing CpG motif.

In view of the complete absence of any guidance relating the claimed invention and the different immunostimulatory activities that is observed in the specification, the skilled artisan cannot possible practice the claimed invention without extreme research and experimentations. **To practice the claimed invention, the skilled artisan would have to conduct extensive research and experimentation**.

Thus, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat bacterial infections; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of

cytokines; the skilled artisan cannot possibly practice the claimed invention without an undue burden of research and experimentation.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/613916.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 19 of the conflicting patent application is directed at the treatment of mycobacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C.

The difference between the two claims is that claim 19 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the generic recitation CpG.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in

the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

The last difference between the two claims is that claim 19 of the conflicting patent application recites mycobacterial infections instead of bacterial infections. However, it is noted that mycobacterial infections is encompassed by the generic bacterial infections.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 10/224523.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 67 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the oligonucleotide is 14-100 residues in length.

The difference between the two claims is that claim 67 limits the length of the oligonucleotide to 14-100 residues in length. However, this length is encompassed by generic recitation oligonucleotide comprising the CpG; wherein the cited recitation does not limit the length of the oligonucleotide.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 10/787737.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 38 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C, and wherein the oligonucleotide is a stabilized oligonucleotide.

The difference between the two claims is that claim 38 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the recitation CpG.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/735592.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 30 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the oligonucleotide comprises the formula: $5'TCGX_1X_3N_13'$.

The difference between the two claims is that claim 30 limits the oligonucleotide to a particular structure. However, the structure that is recited in claim 30 is encompassed by the generic recitation oligonucleotide comprising the CpG motif.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 41 of copending Application No. 10/894682.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 41 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises unmethylated cytosine; the oligonucleotide comprises the formula: $5'X_1X_2CGX_3X_43'$; and the oligonucleotide is associated with a sterol, lipid, and a target cell specific binding ligand.

The difference between the two claims is that claim 41 limits the oligonucleotide to a particular structure. However, the structure that is recited in claim 41 is encompassed by the generic recitation oligonucleotide comprising the CpG motif.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

The other difference between the two claims is that claim 41 of the conflicting patent application requires the oligonucleotide is associated with a sterol, lipid, and a target cell specific binding ligand. However, it should be noted that claim 104of the instant patent application does not exclude this element.

The last difference between the two claims is that claim 41 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the recitation CpG.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. A terminal disclaimer to U.S. Patent No. 6207646 is noted of record.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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